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P.1.031 Dissection of hippocampal CRH-CRHR1 signalling in early life stress-induced learning and memory deficits

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The hippocampus is not only crucially involved in spatial memory formation, but is also highly sensitive to stress. Early adverse experience in children may predispose to later life morbidity, including cognitive deficits. A novel mouse model for early life "psychological" stress by manipulating the cage environment during the first postnatal week has been established, which exhibits profound and long-lasting neuroendocrine and cognitive impairments after stress [1]. Corticotropin-releasing hormone (CRH), the key regulator of the neuroendocrine response to stress, modulates synaptic efficacy and mediates stress-related spine loss in hippocampal neurons, while selective blockade of its receptor CRHR1 has the opposite effect. However, how and to what extent the hippocampal CRH-CRHR1 system contributes to early life stress-related cognitive dysfunction remains unclear.

Recently, the generation of region-specific conditional CRHR1 knockout mice has enabled us to dissect the role of the limbic CRH-CRHR1 system in stress-related cognitive dysfunction. In the present study, we therefore applied the early life stress model by introducing the limited nesting material paradigm to both limbic CRHR1 knockout (CamCRHR1) mice and wild-type littermates. In both Y-maze and Morris water maze tasks, early life stress impaired the performance of hippocampus-dependent spatial learning and memory in stressed wild-type animals ($n = 18$) at 6 months of age compared to control littermates ($n = 20$), while stressed CamCRHR1 mice ($n = 10$) showed similar performance to control littermates ($n = 13$). The spatial memory deficit in stressed wild-type mice was accompanied by impaired LTP in hippocampal CA3 neurons. Moreover, by using in situ hybridization and immunohistochemistry, we found that the expression of specific synaptic cell adhesion molecules that play pivotal roles in synaptic plasticity and memory [2], including nectin-1 and nectin-3, was altered on both gene and protein levels in the hippocampus of stressed wild-type ($p < 0.05$) but not CamCRHR1 mice. Interestingly, nectin-1 and nectin-3 partially colocalized with CRHR1 in mouse hippocampal pyramidal neurons. This points to the possibility that increased CRH-CRHR1 signaling following stress experience may lead to molecular, morphological and functional abnormalities underlying cognitive impairments, while CRHR1 antagonism could prevent these detrimental effects. To support our hypothesis, we then tested basal cognitive performance in both limbic CRH overexpressing (CamCRH) mice ($n = 13$) and wild-type littermates ($n = 13$) at 6 months of age. In the Morris water maze test, adult CamCRH mice showed impaired spatial memory and cognitive flexibility, mimicking the effects of early life stress on cognition. Both mRNA and protein levels of nectin-1 and nectin-3 were decreased in the hippocampus of adult CamCRH mice. In summary, our data suggested that CRH and CRHR1 are crucial regulators of cognitive performance under or after stress conditions, and nectins might be involved in CRH and CRHR1 regulated learning and memory processes.

Reference(s)

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